Sleep Disturbances After Cerebral Infarction: Role of Depression and Fatigue

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Background: Poststroke sleep disturbances (PSSDs) are frequent and reported to be associated with unfavorable clinical outcomes. PSSDs appear to be related to a multitude of factors including lesion location and environmental causes. Moreover, depression and fatigue, which frequently develop in stroke patients may also contribute to PSSD development. The purpose of this study was to evaluate the prevalence and characteristics of PSSDs and factors related to PSSDs including depression and fatigue in hospitalized stroke patients. *Methods:* Patients who were hospitalized with acute stroke at the Asan Medical Center were evaluated. The quality (Verran–Snyder-Halpern [VSH] Sleep Scale score), duration and latency of night-time sleep, the frequency of waking after sleep onset, and daytime sleepiness were evaluated during the hospitalization period. To validate the self-reported night-time sleep, an actigraphy was performed in a subset of patients. The location, circulation, and laterality of each lesion were determined from brain magnetic resonance images obtained within 7 days of stroke onset. Depression and fatigue were assessed using the Beck Depression Inventory and the Fatigue Severity Scale, respectively. For environmental factors, the duration of hospitalization and the number of other patients in the same room were recorded. Univariate, multiple regression, and multiple logistic regression analyses were used to evaluate predictors of PSSD development. *Results:* A total of 282 patients completed the study. The mean age of the patients was 62.3 (±12.76) years and 58.9% of them were male. Sixty patients (21.3%) reported sleep duration less than 6 hours/night and 110 (39.0%) reported more daytime sleepiness than before the stroke. In 54 patients who agreed to wear an actigraph, self-reported sleep duration was significantly correlated with time in bed measured with an actigraph ($r = .407$, $P = .002$) and, VSH Sleep Scale score and sleep efficiency in actigraphy were also significantly correlated ($r = .305$, $P = .026$). Quality of night-time sleep was independently related to cortical lesion location ($P = .002$), diabetes mellitus ($P = .020$), and depression ($P < .001$), whereas increased daytime sleepiness was independently associated with subcortical lesion location ($P = .031$), fatigue ($P = .001$), and quality of night-time sleep ($P = .001$). *Conclusions:* PSSDs are common in hospitalized stroke patients. The most powerful factor predicting night-time sleep disturbances in stroke patients was depression. Cortical brain lesion and diabetes mellitus were also associated with night-time sleep disturbances. On the other hand, although poststroke daytime sleepiness is in part caused by night-time sleep disturbance, it is more closely associated with fatigue and subcortical lesion location. **Key Words:** Sleep—stroke—sleepiness—fatigue—depression.

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Introduction

Poststroke sleep disturbances (PSSDs) are common sequelae of stroke, and occur in 40%-80% of stroke patients.[1,2] PSSDs are frequently disabling and unfavorably associated with neurologic recovery[3] and poor quality of life.[4] Nevertheless, PSSDs, especially nonbreathing-related PSSDs, have scarcely been studied in stroke patients.[5]

PSSDs are related to physical disability, dementia, psychotropic drug usage,[1] and may also be related to lesion location.[6] However, PSSDs could also be caused by depression or fatigue that frequently develops in stroke patients.[7,8] Environmental factors, including noise, light, and monitoring systems, may also contribute to the development of PSSDs. Nevertheless, few studies have comprehensively investigated the prevalence of and factors related to PSSDs in hospitalized stroke patients.

The purpose of this study was to evaluate the prevalence and characteristics of PSSDs in hospitalized stroke patients. In addition, we evaluated the possible roles of patients' depression and fatigue as well as the lesion location, neurologic dysfunction, and environmental factors in the development of PSSDs.

Materials and Methods

Patients

All patients who were admitted to the Asan Medical Center with a diagnosis of acute ischemic stroke between March 2009 and February 2010 were prospectively enrolled. Diagnosis was confirmed using brain magnetic resonance images obtained within 7 days of stroke onset. Because of the one-on-one interview method, which was used for data collection, patients were excluded if they had communication problems (decreased consciousness, confusion, aphasia, dementia, or dysarthria) severe enough to preclude a reliable interview and a significant medical condition. Patients were also excluded if they were taking medications, including sleeping pills or sedatives and had a pre-existing insomnia or narcolepsy that had been diagnosed by a medical doctor because these conditions could have a confounding influence on sleep disturbance after stroke onset. The Institutional Review Board of the Asan Medical Center approved this study, and all enrolled patients provided written informed consent.

To avoid any possible effects of acute unstable neurologic condition on sleep patterns, the interview with each patient was conducted after they had been neurologically stabilized (mean, 6.7 ± 1.89 days after the onset of stroke). For this reason, interviews for patients admitted to neurointensive units or the stroke unit were delayed until they were transferred to a general neurologic ward. The interview included questions regarding PSSDs, depression, and fatigue. The hospital allows the relatives of stroke patients in general neurologic wards to remain at the bedside for 24 hours/day. Therefore, most interviews (n = 274) were conducted in the presence of relatives, who confirmed the responses given by the patient. When relatives were not present during the interview (n = 8), patients' responses were confirmed by calling relatives who had stayed overnight with the patient during hospitalization.

On admission, an experienced stroke neurologist recorded the National Institutes of Health Stroke Scale score. The location, circulation, and laterality of each lesion were determined from magnetic resonance images by one of the authors (J.S.K.) who was blinded to the sleep-interview results. Location was categorized as cortical (anterior or posterior), subcortical (thalamus, corona radiata, basal ganglia, or internal capsule), brainstem (pons/midbrain/medulla), or cerebellum. The lesion location was defined as anterior cortical if the lesion was in the anterior cerebral artery territory or the frontal and parietal areas of the middle cerebral artery territory, whereas posterior cortical location was defined if the lesion was in the occipital area or medial temporal area of the posterior cerebral artery territory. Circulation and laterality of the lesions were divided into anterior/posterior/both and right/left/both, respectively.[9,10] Stroke subtypes were classified as large-artery atherosclerosis, small-vessel occlusion, cardioembolism, and others according to the Trial of Org 10172 in Acute Stroke Treatment.[11] The presence of metabolic syndrome was defined based on the National Cholesterol Education Program Adult Treatment Panel III.[12] The duration of hospitalization and the number of other patients in the same room (either 1 or 5 other patients) were also recorded. The duration of hospitalization was categorized as greater than 5 days or 5 days or less.

Assessment of Poststroke Depression and Fatigue

Depression was considered to be present if the Beck Depression Inventory score was greater than 13 or if the patient met the criteria of the Diagnostic and Statistical Manual, fourth edition,[13] that had been modified to omit criteria dependent on symptom duration of 2 weeks.

For fatigue assessment, the Fatigue Severity Scale (FSS) was used. The FSS consists of 9 items, each scored on a 7-point Likert scale. The FSS score is calculated as an average of the 9 items, with higher scores indicating more severe fatigue. A score equal to 4 or more was considered as clinically significant fatigue.[14]

Assessment of Night-time Sleep

The Verran–Snyder-Halpern (VSH) Sleep Scale[15] was used to evaluate the overall quality of sleep. This 8-item scale evaluates multiple aspects of sleep on a visual analog scale ranging from zero ('very bad') to 10 ('very good'). The VSH Sleep Scale score is calculated as the

sum of the 8 item scores, with higher scores indicating better quality of sleep. Three further questions were asked to characterize sleep duration, sleep latency, and the frequency of waking after sleep onset: (1) "How many hours of sleep do you get at night during hospitalization?" (2) "How many minutes does it take you to fall asleep at the hospital?" (3) "How many times do you wake up at night?" Sleep duration was categorized as greater than 8 hours, 6-8 hours, or less than 6 hours.[16] Sleep latency was categorized as greater than 20 minutes or 20 minutes or less.[17] The presence of sleep apnea and snoring were assessed by asking the close relative who slept with the patient at the hospital: "How often does the patient stop breathing at night?" and "How often does the patient snore at night?" respectively. The patients/relatives were asked to answer every day/occasionally/none to each question.

To validate the self-reported details of night-time sleep, actigraphy was performed in the patients who agreed to wear an actigraph (Ambulatory Monitoring Inc, Ardsley, NY) for 3 days to measure sleep efficacy and time in bed.[3] Actigraphs were provided to the patients on the day of interview. Sleep efficacy and time in bed were averaged and correlated with quality of night-time sleep and sleep duration, respectively.

Assessment of Daytime Sleep

Daytime sleepiness was evaluated by asking if the patient had a greater tendency to sleep in the daytime after the stroke than they did before the stroke. For further evaluation of daytime sleep, they were asked to report the average duration and frequency of daytime naps during the period of hospitalization.

Statistical Analysis

All analyses were performed with SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). In the patients who wore the actigraph, the self-reported details of night-time sleep (VSH Sleep Scale score, sleep duration) were correlated with the actigraphically measured characteristics (sleep efficiency, total sleep time) using the Spearman correlation coefficient. Analysis of variance and t tests were used to compare the VSH Sleep Scale score, sleep duration, sleep latency, the frequency of waking after sleep onset, and frequency and duration of daytime sleep across patients with each clinical characteristic. Chi-square tests were used to compare the presence of increased daytime sleepiness after stroke across patients with each clinical characteristic. Multiple regression analysis was used to determine factors that were independently related to night-time sleep (VSH Sleep Scale score, sleep duration, sleep latency, and the frequency of waking after sleep onset) and daytime sleep (frequency and duration). Logistic regression was used to determine the factors that were related to the presence of increased daytime sleepiness. In multiple regression and logistic regression analyses, age, gender, and all factors that were significant in the univariate analysis ($P < .05$) were included. The level of statistical significance was set at P less than .05 for all analyses.

Results

Three hundred thirty-eight patients were admitted to the Department of Neurology, Asan Medical Center, with a diagnosis of acute stroke between March 2009 and February 2010. Forty-nine patients were excluded: 24 because of pre-existing sleep disorders and 25 because of taking sedatives and/or sleeping medications, such as barbiturates and benzodiazepines. The remaining 289 patients provided informed consent and were enrolled in the present study. Among 289 patients, 7 withdrew from the study during the interview process because of difficulties in finishing the interview itself. The NIHSS score at admission was not different between the patients who participated (mean, 3.88 ± 3.11) and those who did not (mean, 4.11 ± 1.97) ($P = .795$). Data were analyzed from the 282 consecutive patients who completed the study. Demographics, clinical characteristics, and descriptive statistics of PSSDs in the patients are shown in Table 1. The mean ± standard deviation of sleep duration was 7.10 ± 2.08 hours and sleep latency was 20.0 ± 21.2 minutes.

In 54 patients who agreed to wear an actigraph, actigraphies were performed for 2.8 (±.41) days. Eleven patients wore the actigraphs for 2 days because of early discharge. Self-reported sleep duration was significantly correlated with time in bed measured with an actigraph ($r = .407$, $P = .002$), and VSH Sleep Scale score and sleep efficiency in actigraphy were also significantly correlated ($r = .305$, $P = .026$).

In univariate analysis, the VSH Sleep Scale score was significantly lower in patients with diabetes mellitus ($P = .022$), depression ($P < .001$), and fatigue ($P = .006$). Hypertension, hyperlipidemia, metabolic syndrome, and stroke subtypes were not associated with VHS Sleep Scale score. Patients with cortical lesions had a lower VSH Sleep Scale score than patients with lesions in other area ($P = .049$). Sleep duration was shorter in patients who were hospitalized for 5 days or less than that in patients who were hospitalized for more than 5 days ($P < .001$). Sleep latency was longer in patients with depression ($P < .001$), whereas the frequency of waking after sleep onset was greater in patients with depression ($P = .023$) and fatigue ($P = .010$). The presence of increased daytime sleepiness was higher in patients with subcortical lesions ($P = .005$), fatigue ($P < .001$), and poorer quality of night-time sleep ($P < .001$). The frequency of daytime sleep was greater in patients with subcortical lesions ($P = .001$), previous stroke ($P = .033$), and fatigue ($P < .001$). The duration of daytime sleep was greater in patients with

Table 1. *Demographics, clinical characteristics, and descriptive statistics of PSSDs in all patients who completed the study (n = 282)*

Variable	Mean ± SD or n (%)
Demographics	
Age (y)	62.34 ± 12.76
Gender	
Male	166 (58.9)
Clinical characteristics	
NIHSS score at admission	3.88 ± 3.10
Lesion location	
Anterior cortex	41 (14.5)
Posterior cortex	39 (13.8)
Thalamus	35 (12.4)
CR, BG, or IC	83 (29.4)
Pons and midbrain	41 (14.5)
Medulla	14 (5.0)
Cerebellum	29 (10.3)
Circulation	
Anterior	151 (53.5)
Posterior	123 (43.6)
Both	8 (2.9)
Laterality	
Right	144 (51.1)
Left	124 (44.0)
Bilateral	14 (5.0)
Stroke subtype	
Large artery disease	105 (37.2)
Small artery disease	78 (27.7)
Cardiogenic	47 (16.7)
Others	52 (18.4)
History of previous stroke	51 (18.1)
Hypertension	191 (67.8)
Diabetes mellitus	79 (28.0)
Hyperlipidemia	
Yes	124 (44.0)
Metabolic syndrome	
Yes	107 (37.9)
Depression	33 (11.7)
Fatigue	69 (26.3)
Snoring	
Always	138 (49.0)
Occasionally	69 (24.6)
None	75 (26.6)
Sleep apnea	
Always	76 (26.9)
Occasionally	119 (42.3)
None	87 (30.8)
Duration of hospitalization ≤5 d	163 (57.8)
No. of patients sharing the room	
One person	133 (47.2)
Five persons	149 (52.8)
Descriptive statistics of PSSDs	
Verran–Snyder-Halpern Sleep Scale score	58.3 ± 15.05
Sleep duration	
<6 h	60 (21.3)
6-8 h	154 (54.6)
>8 h	68 (24.1)
Sleep latency >20 min	84 (29.8)
Frequency of waking after sleep onset	1.89 ± 1.67
Increased daytime sleepiness after stroke	110 (39.0)
Frequency of daytime sleep	1.29 ± 1.36
Duration of daytime sleep (min)	37.1 ± 44.65

Abbreviations: BG, basal ganglia; CR, corona radiata; IC, internal capsule; NIHSS, National Institutes of Health Stroke Scale; PSSDs, poststroke sleep disturbances; SD, standard deviation.
Data are the mean ± standard deviation or n (%).

previous stroke (P = .036), depression (P = .025), and fatigue (P = .042). Duration of hospitalization and the number of other patients in the room were not related to daytime sleep characteristics. Neither snoring nor sleep apnea was related to night-time and daytime sleep.

In multiple regression analysis, cortical lesion location (P = .002), diabetes (P = .020), and depression (P < .001) were independently associated with the VSH Sleep Scale score (Table 2). The presence of depression was independently associated with sleep latency (P < .001) and the frequency of waking after sleep onset (P = .038).

The factors independently related to the presence of increased daytime sleepiness in multiple logistic regression analysis were subcortical lesion location (P = .031), fatigue (P = .001), and VSH Sleep Scale score (P = .001) (Table 3). Fatigue (P < .001) was also related to the frequency of daytime sleep, whereas older age (P = .002) was associated with the average duration of daytime sleep in multiple regression analysis. Subcortical lesion location (P = .043) was also significantly related to the frequency of daytime sleep.

Discussion

This study investigated PSSDs in hospitalized stroke patients. Our results indicated that 21% of patients reported that they slept less than 6 hours, which is less than the duration of sleep considered to be normal in the elderly (6-8 hours).[18,19] This result is consistent with a previous report that 21% of stroke patients reported insomnia or short sleep duration at night,[20] but lower than other reports of a 68%-78% incidence of insomnia in hospitalized stroke patients.[2,21] The relatively lower prevalence may be because of a difference in the methods used to quantify sleep disturbances and differences in characteristics of subjects; we excluded patients with

Table 2. *Results of multiple regression analysis of the factors related to night-time sleep in 282 stroke patients*

Variable	B	SE	β	t	P
Verran–Snyder-Halpern Sleep Scale score					
Constant	52.73	6.474		8.145	.000
Age	.056	.075	.047	.745	.457
Gender	−.136	1.900	−.004	−.072	.943
Brainstem lesion location (reference)					
Subcortical lesion location	−1.717	2.607	−.056	−.695	.511
Cortical lesion location	−8.268	2.699	−.248	−3.063	.002
Cerebellar lesion location	−5.084	3.629	−.101	−1.401	.163
Diabetes mellitus	4.943	2.108	.144	2.345	.020
Depression	−14.12	2.961	−.296	−4.769	.000
Fatigue	−2.831	2.156	−.082	−1.313	.190
Sleep latency					
Constant	67.65	15.25		4.435	.000
Age	−.035	.145	−.014	−.241	.810
Gender	−2.174	3.778	−.034	−.575	.565
Depression	−22.470	5.701	−.231	−3.942	.000
Frequency of waking after sleep onset					
Constant	1.628	.615		2.647	.009
Age	−.005	.009	−.038	−.602	.548
Gender	.117	.237	.032	.494	.622
Depression	.573	.274	.137	2.091	.038
Fatigue	.471	.377	.082	1.250	.213

Abbreviation: SE, standard error.

severe strokes (eg, those with decreased consciousness, communication problems, significant medical conditions, and those who were in neurointensive or stroke units and could not be transferred to general wards) and those with pre-existing sleep disorders.

We found that depression was independently related to the overall quality of sleep at night, evaluated using the VSH Sleep Scale. Particularly, depression was closely related to delayed latency of sleep onset and frequent awakening after sleep. Therefore, depression seems to be one of the important causes of sleep disturbances in hospitalized stroke patients. However, this relationship may be in part because of the inherent problem of definition: diagnostic items of depression contain poor quality of sleep.[7] Moreover, the association may be related to similar location or laterality of brain lesion producing depression and sleep problems; we found that quality of sleep at night was poorer in patients with lesions in the cortical area than in those having other lesions. Previously poststroke depression has been reported to be most pronounced in patients with lesion in the left cerebral hemisphere and/or anterior cortical lesions.[13,22] Interestingly, the location of a lesion in the cortex of the brain was independently associated with poor quality of sleep. Further analysis revealed that patients with left-sided cortex lesion had more frequent awakenings at night. A previous study also suggested a link between cortical infarction and PSSDs, particularly between frontal lobe lesion and insomnia.[23] However, the association between lesion laterality and PSSDs has yet to be reported. Further evidence suggesting the involvement of the cerebral cortex in PSSDs comes from a report of decreased total sleep time in patients with Pick's dementia, which is characterized by frontal and temporal lobe atrophy.[24]

We found that diabetes mellitus was another independent predictor of night-time sleep quality. Previous studies have shown an association between diabetes and sleep disturbance in the general population.[25-27]

Table 3. *Results of logistic regression analysis of the factors related to increased daytime sleepiness after stroke in 282 stroke patients*

Variable	B	SE	P	Exp (B)
Constant	.988	1.012	.329	2.686
Age	.002	.012	.856	1.002
Gender	−.423	.300	.158	.655
Cortical lesion location (reference)				
Subcortical lesion location	.774	.359	.031	2.169
Brainstem lesion location	−.941	.499	.059	.390
Cerebellar lesion location	.458	.517	.376	1.580
Fatigue	1.092	.327	.001	2.981
Verran–Snyder-Halpern Sleep Scale score	−.033	.010	.001	.967

Abbreviation: SE, standard error.

The association may be because of the higher rate of sleep apnea in patients with diabetes.[28] However, in our further analysis, there was no association between the presence of diabetes and sleep apnea or snoring (data not shown). Night-time sleep disturbance in patients with diabetes may result from the activation of the hypothalamic pituitary adrenal axis and sympathetic system in these patients,[29,30] which may lead to physiological hyperarousal and shorter sleep duration. In addition, it could be because of the severity of sleep apnea.[31,32] Although we could not assess the severity of sleep apnea in our patients, patients with both diabetes and stroke may have severer sleep apnea, which may have decreased the quality of night-time sleep.[33,34]

In our study, the presence of metabolic syndrome was not significantly related to quality of night-time sleep, which is contrary to previous results.[35,36] The discrepancy may come from the differences in study subjects. Previous studies enrolled healthy adults who had all components of metabolic syndrome even, whereas majority of our patients (85.7%) with metabolic syndrome had elevated blood pressure, which was reported to have little relevance to sleep quality.[37] In our further analysis, hypertension was not related to quality of night-time sleep. Therefore, night-time sleep may not be significantly related to metabolic syndrome at least in stroke population in whom hypertension is a dominant risk factor.

As expected, we found that increased daytime sleepiness after stroke was related to poor quality of sleep at night (Table 3), suggesting that the latter is the cause of the former. However, we found that there are still other independent factors: daytime sleepiness was closely related to fatigue. A close association between fatigue and daytime sleepiness has also been observed in patients with multiple sclerosis.[38] Although the cause–effect relationship remains unclear, fatigue may be one of the causes of daytime excessive sleepiness in stroke patients. Interestingly, excessive daytime sleepiness was closely related to subcortical lesion location. This result is consistent with a previous report that there is an excessive sleepiness in patients with subcortical stroke.[39] This may be because of an interruption to the arousal systems, including the ascending reticular activating system,[40] caused by lesions in these locations. Severe and persisting forms of dearousal were reported in patients with bilateral lesions of the thalamus, subthalamic area, and brainstem where fibers of the ascending reticular activating system were severely injured.[6] Therefore, daytime sleepiness may be a multidimensional phenomenon that results from patients' poor quality of sleep at night, fatigue, and brains' structural dysfunction related to arousal system.

Contrary to the results of previous studies,[41,42] we found no association between sleep disturbances and the hospital environment. Sharing a room with 5 other patients and their caregivers may be expected to be associated with increased noise, light, and medical monitoring, which all may interfere with sound sleep at night. However, sharing a room with 5 people was not associated with sleep disturbances. Duration of hospitalization also did not affect the quality of sleep, suggesting that depression and lesion location outweigh environmental factors in determining the quality of sleep at night during hospitalization.

Our study has limitations. The sleep characteristics analyzed in this study were determined from self-reported data, and not based on objective studies such as polysomnography. However, the close association between self-reported data and actigraph data in a subset of patients indicates that the information we obtained was relatively accurate because actigraphy-scored sleep was known to be consistent with sleep measured using polysomnograph.[43] In addition, it is possible that we have underestimated the prevalence of PSSDs, as we excluded patients with communication problems, significant medical conditions, and pre-existing sleep disorders.

Despite these limitations, our results show that PSSDs are common in hospitalized stroke patients. Night-time sleep disturbances were associated with depression and cortical infarction, whereas increased daytime sleepiness was associated with infarction in subcortical areas of the brain and fatigue in addition to night-time sleep disturbances.

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